Repotrectinib, a next generation TRK inhibitor, overcomes TRK resistance mutations including solvent front, gatekeeper and compound mutations

**Abstract**

Oncogenic TRKα/B/C fusion isoforms are identified in various cancer types in adults and children. TRK inhibitors (TRKis) have demonstrated marked efficacy in patients with cancers, however acquired on-target resistance mediated by kinase domain mutations can occur. Next-generation TRKIs targeting both wildtype and mutant TRK fusions can potentially address this unmet medical need. Repotrectinib was designed to potently inhibit wildtype (WT) TRK and overcome resistance mutations. The anti-proliferative activity of 1st generation (larotrectinib-entrectinib) and next-generation (repotrectinib/LO XO-195) TRKIs were compared using engineered Ba/F3 cells expressing WT or mutated TRKs. Repotrectinib was over 10-fold more potent than LOXO-195, against WT TRK and solvent front fusions (SFMs), and more than 100-fold more potent against the gatekeeper mutations TRKA(F589L) and TRKB(F636L). Furthermore, repotrectinib was the only TKI active against the compound mutation TRKA(G595R/597D) in cis to pTyr204 in Ba/F3 cells. In xenograft mouse models, repotrectinib treatment led to significant tumor regression in tumors carrying WT or mutated TRK fusion kinases. In the ongoing TRIDENT-1-1 clinical trial of repotrectinib (NCT0393116), the SFMs TRKA(G595R), TRKB(G636R) and TRKC(G638E) and the gatekeeper mutation TRKA(F589L) were detected in plasma ctDNA samples at baseline from three TRK-resistant patients. Repotrectinib was active against ETF6-TRK(G633E) in an entrectinib resistant patient with a salivary gland tumor who achieved confirmed partial response with 9.8 months of duration of response. Tumor regression was also observed in a cholangiocarcinoma patient with LMNA-TRKA(F589L) and F588L in mutations in trans. TRIDENT-1 is currently enrolling NTRK-fusion-positive patients with advanced solid tumors (NCT0393116).

**Introduction**

Clinical resistant mutations in TRKA.

- The TRK histogram includes TRKA, TRKB, and TRKC proteins encoded by the genes NTRK1, NTRK2, and NTRK3, respectively.
- Oncoenic TRK fusions that lead to constitutive activation of TRK signaling have been identified in many solid malignancies in both adults and children.
- 1st generation TRK inhibitors including larotrectinib and entrectinib have demonstrated clinical benefit in patients with solid malignancies harboring oncoenic NTRK fusions.
- Solvent front mutation, gatekeeper and glycine mutation of DFG at the beginning of the A-loop have been reported in clinical trials from larotrectinib- and entrectinib-reactor patients.
- Repotrectinib was designed to systematically overcome resistant mutations.

**Repotrectinib poinetly inhibited WT and mutant TRK**

**Case 1**

- **17 year-old Asian male**
  - Diagnosed with metastatic salivary gland cancer in 2013
  - Started on oral dose of 30 mg QD and later escalated to 80 mg QD
  - Dosed at the same dose level of 30 mg/kg BID with statistically significant response as PR
- **195) TRKis were compared using engineered Ba/F3 cells and found to be 7.3 months, PR), and followed by the combination of entrectinib+MEK therapy (cPR, data based on evaluation of comparable proxy chemical reagents purchased from commercial sources. WT: wildtype
- **Repotrectinib was designed to bind completely inside the ATP pocket of the target kinase with the capability of targeting both wild type and mutant kinases.**
- **Repotrectinib is the most potent TRK inhibitor against both wildtype and mutated TRKs, including G595R solvent front, F589L gatekeeper, and LMNA compound mutations.**
- **Repotrectinib was more effective than LOXO-195 when dosed at the same dose level of 30 mg/kg BID with statistically significant change of tumor volume (p = 0.003) in the model carrying the LMNA TRKA(G595R/597D) compound mutation.**

**References**


**Repotrectinib clinically inhibits resistant tumors**

**Figure**

- Repotrectinib was designed to bind completely inside the ATP pocket of the target kinase with greater precision and affinity and is able to target both wild type and mutant kinases.
- Repotrectinib potently inhibited WT and mutant TRKs in vitro and in vivo, including the solvent front mutations which render common resistance to TRK inhibitors larotrectinib and entrectinib.
- Repotrectinib is the most potent TRK inhibitor against both wildtype and mutated TRKs, including solvent front, gatekeeper, and compound mutations in comparison with other TRK inhibitors.
- Repotrectinib demonstrated antitumor effectiveness in refractory patients treated with generation TRK inhibitors.

**Conclusions**

- **Repotrectinib was designed to bind completely inside the ATP pocket of the target kinase with greater precision and affinity and is able to target both wild type and mutant kinases.**
- **Repotrectinib potently inhibited WT and mutant TRKs in vitro and in vivo, including the solvent front mutations which render common resistance to TRK inhibitors larotrectinib and entrectinib.**
- **Repotrectinib is the most potent TRK inhibitor against both wildtype and mutated TRKs, including solvent front, gatekeeper, and compound mutations in comparison with other TRK inhibitors.**
- **Repotrectinib demonstrated antitumor effectiveness in refractory patients treated with generation TRK inhibitors.**

**Phase 1/2 clinical trial (TRIDENT-1) of repotrectinib is on-going for patients with advanced solid tumors harboring a ROS1, NTRK, or ALK fusion gene (NCT0393116)**

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